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Role of dietary fibre in older adults with asymptomatic (AS) or symptomatic uncomplicated diverticular disease (SUDD): systematic review and meta-analysis

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Dietary fibre and probiotics may play a role in the management of diverticular disease. In adults with asymptomatic (AS) or symptomatic uncomplicated diverticular disease (SUDD), this systematic review aims to synthesize evidence on the efficacy of dietary fibre modifications, with or without the use of probiotics, on gastrointestinal function, symptoms, and diverticulitis incidence. Five electronic databases were searched for studies until December 2018. The body of evidence was appraised using the Cochrane Risk of Bias tool and GRADE. Nine studies were included with mean sample ages ranging from 57 to 70 years, and three meta-analyses were performed. Only one study, with high risk of bias, measured the effect of dietary fibre on diverticulitis incidence. Dietary fibre supplementation was found to improve stool weight (MD: 42g/day, $P<0.00001$; GRADE level of evidence: low), but had no significant effect on gastrointestinal symptoms (SMD:-0.13, $P=0.16$; GRADE level of evidence: low) or stool transit time (MD:-3.70, $P=0.32$ GRADE level of evidence: low). There was “very low” confidence for the body of evidence supporting symbiotics for AS or SUDD. A high dietary fibre intake, in line with dietary guidelines, may improve gastrointestinal function and is recommended in patients with AS or SUDD. Dietary fibre supplementation should be considered on an individualised basis to improve bowel function, while the recommendation for symbiotic supplements requires further well-designed research. Future studies should also measure impact on the incidence of diverticulitis.

Keywords: dietary fibre; diverticulitis, diverticular disease, systematic review; probiotics; symbiotic

Introduction

Diverticulitis is one of the most common and costly gastrointestinal disorders, primarily presenting in older adults [1-6]. Diverticulitis is a complication of diverticulosis, a condition defined by the presence of colonic diverticula, which are mucosal herniations in the muscle layer of the colon wall [7]. Diverticulosis can present itself as asymptomatic (AS) diverticular disease or as symptomatic uncomplicated diverticular disease (SUDD). SUDD differs from AS in that the herniations are associated with persistent gastrointestinal symptoms (GIS) similar to that of irritable bowel syndrome, such as flatulence, pain, faecal urgency, bloating, and altered bowel function for at least three months without acute inflammation [8, 9]. Due to the overlap in both pathogenesis and symptoms between SUDD and irritable bowel syndrome, misdiagnosis is common [10]. Signs of acute inflammation of the diverticula are indicative of diverticulitis, which presents with acute, severe GIS including abdominal pain, tenderness, fever, and/or altered bowel function [11]. Diverticulitis cases may develop sepsis, pelvic ulcers, haemorrhages, and perforations. Often an episode of diverticulitis is the trigger for an accurate diagnosis of AS or SUDD, whereas symptoms previously may have been considered to be due to irritable bowel syndrome [10]. For this reason, studies with patients diagnosed with AS or SUDD often have samples where participants have had one or more episodes of diverticulitis in the past.

Risk factors for diverticular disease include ageing, adiposity, sedentary lifestyles, and diet, specifically dietary fibre intake [12-14]. Prospective cohort studies have identified a link between overall dietary fibre intake and primary prevention of both diverticulosis and diverticulitis, where adults with the highest intakes of dietary fibre had approximately 40% decreased relative risk of diagnosis [15-17]. The influence of dietary fibre intake on diverticular disease is suggested to be due to its influence on bowel health and function, particularly influencing the risk of constipation, which may in turn influence the risk of infection and

inflammation of the diverticula [18, 19]. Insoluble dietary fibres can act as a prebiotic as they may be fermented by gut microbiota to optimise bacterial fatty acid production that reduces inflammation and supports the growth of functioning of beneficial gut bacteria to strengthen the colonic wall [20-22]. Combining prebiotics with probiotics (beneficial live bacteria) as a symbiotic for diverticulitis prevention is of interest, they might counteract the altered gastrointestinal microflora associated with the disease to improve functioning of the intestine [20].

Despite the important role dietary fibre has in bowel function, General Practitioners do not regularly recommend dietary fibre modifications as a treatment of AS or SUDD, reflecting the lack of intervention evidence currently available [23]. Dietary fibre and probiotics have been examined for diverticular disease in four systematic reviews previously; in addition to the inclusion of more recent published literature, the previous reviews were limited by the relatively poor quality of included studies (i.e. lack of randomised blinding and placebo control), inadequate specification of probiotic strains, narrow search strategies, and failing to examine outcomes related to GIS or bowel function [24-28].

Therefore, there is currently a gap in the literature regarding the role of dietary fibre on AS and SUDD management. In adults with AS or SUDD, this systematic review aims to synthesize evidence on the efficacy of dietary fibre modifications, with or without the use of probiotics, on gastrointestinal function, symptoms, and diverticulitis incidence.

Methods

This systematic review has been reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [29]. The full search strategy is shown in Online Supplementary Material 1. Briefly, Medline (PubMed), Embase, The Cochrane Library, Web of Science, and CINAHL were searched for intervention studies of any

design from database inception up until 12th December 2018 and were complemented by a snowball search of Google Scholar and reference lists of similar review articles.

Eligibility criteria

Studies in any language were included if they included adults (≥ 18 years) with current diagnosis of diverticular disease (as older studies do not often specify if participants had AS or SUDD), AS, or SUDD, who received dietary or supplemental fibre modifications (either a decrease or increase in dietary fibre intake) with or without probiotic administration. Due to the unavailability of CT diagnosis in many settings, this was not a requirement for eligibility; therefore, participants were considered as having diverticular disease, AS, or SUDD if diagnosed by any assessment method. Studies were excluded from this review if a medication likely to affect gut functioning (antibiotic, laxative or anti-inflammatory) was co-administered as part of the intervention or used as a comparator if the intervention didn't also use the same drug.

Observational studies, reviews, abstracts, study protocols, and conference papers, or those that did not report on any outcome of interest were excluded from this review. Studies that assessed primary prevention (diverticular disease development in healthy populations) were excluded. Studies which addressed tertiary prevention (acute diverticulitis treatment) were excluded and reported elsewhere [30]. Screening of titles, abstracts and full-texts was completed by four investigators independently ([FE or MC] and [CD or SM]).

Outcomes of interest

To reflect occurrence of acute diverticulitis, the primary outcome of interest was the incidence of acute diverticulitis, defined as the presence of acute inflammation in diverticula with or without sepsis and other complications. Secondary outcomes of interest were healthcare use

(outpatient visits, hospitalisation, health care costs), GIS, bowel habits, complications (treatment failure of diverticulitis, abscess, perforation or haemorrhaging, requiring drainage or surgery), and participant quality of life.

Review of study quality and confidence in the body of evidence

Using the Cochrane risk of bias tool, study quality was assessed independently by three researchers (CD and [MC or SM]); and reviewed for accuracy by a third researcher (MC or SM) [31]. Two authors independently assessed the certainty in the body of evidence and developed recommendations for populations using GRADE [32], as outlined by the GRADE Handbook [33] and implemented using the software GRADEpro GDT [GRADEpro Guideline Development Tool, McMaster University, 2015; developed by Evidence Prime, Inc].

Data extraction and meta-analysis

Outcome scores and mean change from baseline for both groups were extracted. All data extraction was conducted by one researcher (CD or MC), and all extracted data were checked for accuracy by a senior researcher (SM). Where two or more studies had clinical homogeneity and reported data in enough detail, data were pooled by meta-analysis using Review Manager [Review Manager 5, Version 5.3, 2014, Cochrane Informatics & Knowledge Management Department] using random effects models. The pooled categorical outcomes were reported using risk ratio with 95% confidence intervals, using the Mantel-Haenszel test. Pooled continuous outcomes were reported as mean differences (MD), where the same outcome assessment tool and scale was used. Where standard deviations weren't reported by the original study, they were calculated by Review Manager using the outcome, participant number and P-values ($P=0.05$ used if reported as not significant). Statistical significance for meta-analyses was considered at $p<0.05$.

Results

Search results and study quality

The search strategy located 8,326 records and a further 13 studies were identified by snowball searching (Figure 1). After title and abstract screening, the full-text of 141 studies were considered and nine studies published between 1972 and 2012 were included (Table 1). Four studies (with a total of five intervention arms) were included in three meta-analyses [34-37].

The Cochrane risk of bias tool indicated most studies had either high or unclear risk of bias for most domains (Figure 2; justifications in Online Supplementary Material 2). One of the most common causes of risk of bias across the body of evidence was the lack of objective and/or validated subjective measures in regards to GIS; and a lack of blinding which is particularly problematic given the susceptibility of self-perceived GIS to the placebo effect [38]. Other bias of major concern is the large number of studies which were funded by pharmaceutical and/or supplement companies, that had undescribed involvement in the studies, combined with incomplete data reporting which tended to favour the product investigated. Furthermore, most studies either did not use randomisation or concealed allocation, or it was not described with sufficient detail to determine if it was well implemented. Due to the small number of included studies for each outcome combined in meta-analyses, publication bias could not be evaluated.

Characteristics of included studies

Six studies were randomised controlled trials (comprising n=3 RCT, n=3 cross-over RCTs) and the remaining three were uncontrolled pre-test post-test trials. One RCT [36] and one cross-over RCT [39] both had two eligible intervention arms (i.e. 3-arm RCT designs). Sample sizes varied from n=10 to n=76 participants and the majority (n=6) were from the United Kingdom. Although the studies did not specifically recruit older adults, all study samples were aged ≥ 60 -

years, excepting one sub-sample aged 57 years [35] and one study which did not report participant age [40]. Therefore, the participants included in this review were considered to meet the United Nations criteria for older adults (≥ 60 years) [41]. The samples in all studies were reported to be diagnosed with SUDD, except for two studies which didn't specify the type of diverticular disease in their samples [34, 35].

Only two studies, both of which used symbiotic interventions, standardised the background diet in participants [39, 42]. Of the seven remaining RCTs which modified total dietary fibre intake via supplemental dietary fibre interventions, five did not describe or control the background diet in any way [34, 35, 37, 43, 44], and the remaining two only controlled the background diet by recommending "habitual intake" to participants. However, the cross-over design may control for the impact of background diet between groups for three of these studies [34-36]. Only the intervention described by Painter et al [43] modified dietary intake through dietary sources; however, the amount of dietary fibre from the diet was not measured, and the study also provided dietary fibre supplements.

Of the five studies (n=6 intervention groups) which provided a dietary fibre intervention without probiotics, four provided wheat bran supplementation (6.7 to 45g/day; 3 to 22 months duration) [36, 37, 40, 43], three provided ispaghula supplementation (7 to 12g/day; 1 to 4 months duration) [34, 36, 44], and one provided methylcellulose (1g, 3 months duration) [35]. The two remaining studies (n=3 intervention groups) provided symbiotics, Lactobacillus (5-billion to 12-billion colony forming units (CFUs)) was provided in a combination with oligosaccharides (prebiotic) for 6-months. [39, 42]

Dietary fibre administration in the prevention of diverticulitis and associated outcomes in populations with asymptomatic or symptomatic uncomplicated diverticular disease

There were seven intervention studies with eight intervention arms (published 1972 – 1992) which evaluated the efficacy of 1-month to 3-years dietary fibre supplementation [34-37, 44-46] (Table 1). One of these studies had two intervention groups [36] and three had no comparator group [44-46].

Dietary fibre administration in the prevention of diverticulitis

The effect of dietary fibre on diverticulitis prevention was assessed by Painter et al [46] with no comparator group which administered an unspecified high dietary fibre diet with two teaspoons of bran supplementation three times per day [46]. Painter et al [46] found 2% of the study population developed diverticulitis over a 39 month follow up period. Due to lack of additional studies, data could not be pooled and GRADE assessment was not completed.

Dietary fibre administration in the improvement of gastrointestinal symptoms

The three studies which implemented a pre-test post-test design with no comparator groups found improvements in GIS and bowel habits from baseline with either ispaghula husk supplementation (7g daily) or high fibre diets and/or wheat bran supplementation (3-45g daily) [44-46] (Table 1). Three studies which compared dietary fibre supplementation versus placebo on GIS (evaluated by a range of un-validated tools) could be pooled [35-37], finding insufficient evidence to reject the null hypothesis (SMD: -0.13 [95%: -0.31 to 0.05]; P=0.16; I²: 33%; n= 4 intervention groups; n= 161 participants) [35-37]. There was “low” confidence in the body of evidence that there is no effect of dietary fibre supplementation on GIS.

Dietary fibre administration in the improvement of bowel function

Two meta-analyses could be performed to examine the impact of dietary fibre on bowel function. A meta-analysis of three intervention groups found that dietary fibre significantly increases daily stool weight compared with placebo (MD: 29g/day [95%CI: 8-51g]; n=3

intervention groups [2 ispaghula husk; n=1 bran]; n=2 studies, n=134 participants) [34, 36]; however, heterogeneity was substantial at I^2 : 65%. When including only ispaghula husk, there was a large effect (MD: 42g/day [95%CI: 26-57g]) with no heterogeneity (Figure 3); however, the analyses was heavily weighted to only one study. The quality of the body of evidence (GRADE assessment) that ispaghula husk increases stool weight indicates there is “low” confidence the estimated effect size is close to the true effect in this patient population (Online Supplementary Material 3).

Meta-analysis of two studies reported there was insufficient evidence to reject the null hypothesis that dietary fibre impacts upon stool transit time (MD: -3.70 [95%CI: -11.06-3.65]; $P=0.32$; I^2 : 0%; n=3 interventions groups; n= 134 participants) [34, 36]. There was “low” confidence in the body of evidence for the effect of dietary fibre on stool transit time, acknowledging a spurious confounding effect of the initial stool transit time on the pooled effect size. A large contributor to the low confidence in the body of evidence for these outcomes is due to risk of bias and the small sample sizes in the included studies (Online Supplementary Material 3).

Other bowel function-related outcomes reported by studies comparing dietary fibre with placebo, but not included in meta-analysis due to lack of consistent data reporting, are described in Table 1; these revealed dietary fibre supplementation improved bowel habits such as stool consistency and stool frequency.

Dietary fibre administration on other outcomes of interest

Only two studies, which had no comparator groups, reported assessment of health service use, meaning data could not be pooled and GRADE assessment was not considered. Painter et al [46] reported 5% hospital admissions over a 39- month follow up period and Brodribb et al [40] reported no participants were admitted to hospital for acute diverticulitis

over an 8- month follow up period. No studies were identified to evaluate the effect of dietary fibre intake on patient quality of life or complications.

Symbiotic supplementation in the prevention of diverticulitis and associated outcomes in populations with asymptomatic or symptomatic uncomplicated diverticular disease

There were two studies (published 2011 and 2012) with three intervention groups which compared a symbiotic supplement against a usual care (i.e. no intervention), where both groups were also advised to follow a high dietary fibre diet (Table 2) [39, 42]. All three interventions used *Lactobacillus* as the probiotic, with dosages ranging from 5-billion colony forming units (CFU) to 12-billion CFUs. The prebiotic agents included in the symbiotic preparations were either 750mg oligosaccharides alone or 700mg oligosaccharides combined with 1240mg arabinogalactan. Symbiotic supplements also contained b-group vitamins or glutamine.

Both studies reported zero incidence of acute diverticulitis across all groups over a six-month follow up (no incidence precluding meta-analysis). The symbiotic supplementation in all interventions reported improvements in GIS. Those assigned a higher dose of probiotic (12-billion CFUs) did not benefit from any additional GIS relief compared to those prescribed a lower dose. The studies failed to report and represent adequate data for the comparator group preventing meta-analysis of GIS, and groups were not compared statistically in any study. GRADE assessment revealed there is “very low” confidence that the reported effect sizes represent the true effect of symbiotic supplementation on GIS in patients with AS or SUDD. This is largely due to a small number of studies examining this outcome, significant risk of bias in the studies, and small sample sizes.

Discussion

In older adults with AS or SUDD, existing guidelines recommend a high fibre diet for the long-term primary prevention of diverticulitis based upon expert opinion and observational cohort studies [47-50]. These associations have not yet been sufficiently addressed by intervention studies, highlighting the need for renewed focus in this area [22]. This review identified seven studies which have explored this dietary management strategy, where only one study, which had a high risk of bias, no comparator group, and was published over 40 years ago, measured the effect on diverticulitis incidence [46]. Therefore, the effect of a high dietary fibre intake on the prevention of diverticulitis in those with AS or SUDD is unknown.

There was some evidence that GIS improve with high dietary fibre intake, although the range of un-validated tools used to measure this outcome makes it difficult to determine whether the result was reliable, reflected by the “low” GRADE assessment for this outcome. Although ispaghula husk supplementation was found to have a large significant effect on increasing daily stool weight, improvement in this outcome alone will not contribute significantly to improved symptomatic management of the condition and is considered beneficial for this patient group from a theoretical perspective only, as stool weight is hypothesised to decrease contact of faecal matter with the colon walls. In addition, there is good evidence that dietary fibres from diverse sources increase stool weight to varying degrees [51]. This could explain the heterogeneity seen by including wheat bran with ispaghula husk in the meta-analysis. Therefore, although heterogeneity was improved by removing wheat bran during sensitivity analysis, the small number of included studies and the heavy weighting for one study in the meta-analysis prevents the recommendation of ispaghula husk over other forms of dietary fibre which have shown to have beneficial effects in other patient groups [51]. Additionally, one study [35] included in the meta-analyses for GIS did not report if their sample was diagnosed with AS or SUDD, which may impact upon the intervention’s ability to improve GIS.

The absence of significant change in stool transit time may be confounded by the spurious effect of the baseline transit time as it appears that those with slow transit times quickened, and vice versa, meaning there is likely some normalising of stool transit times for those with initial short or long transit times. The lack of effect on stool transit time for the whole sample may also be confounded by the type of dietary fibre, where soluble dietary fibres (such as ispaghula husk) are known to increase transit time, while insoluble dietary fibre types (such as bran) decrease transit time [52]. Further research comparing different dietary fibre types in patients with AS or SUDD is warranted, due to each fibre having a unique impact upon stool mass and transit time due to its unique particle size, prebiotic capacity, and chemical composition [51].

Conclusions cannot be drawn regarding the impact of symbiotic supplementation on either risk of acute diverticulitis nor its impact on GIS due to poor study quality which prevents comparison of the intervention group to the control groups. Therefore, although symbiotic administration appears safe and may be beneficial, currently there is “very low” confidence in the body of evidence for symbiotic supplementation for the prevention of diverticulitis.

Implications for practice

Therefore, this review supports a high dietary fibre diet for older adults with AS or SUDD, with consideration given to ispaghula husk supplementation on an individualised basis. This aligns with dietary guidelines, which recommend a high dietary fibre intake, where supplementation is considered if the nutrient target cannot be met by foods alone [53]. Due to limitations in the quality of the evidence, it should be recognised that these recommendations may change with the availability of new high-quality intervention studies.

Implications for future research

The body of evidence located for each outcome is small and generally of poor quality, with most studies having a high risk of bias, warranting future research in the area. Main causes of bias should be addressed and avoided in future randomised controlled trials, including double-blinding and fully describing the randomisation and allocation process. Objective and/or validated outcome measures for GIS are required, and all intervention durations and outcome measures should have suitable timeframes of follow-up relevant to each outcome. Additionally, background diets should be controlled and fully described, as should adherence to the intervention. Future studies with industry and/or pharmaceutical funding should aim to ensure independence and transparency through full disclosure of conflicts of interest as well as full reporting of results in both control and intervention arms.

Limitations

The terminology referring to diverticular disease varied among studies, and it should be acknowledged that due to lack of CT diagnosis, it is possible included samples may have been misdiagnosed. Findings were limited as multiple studies did not report outcome data in full, leading to prevention of meta-analyses for many outcomes, downgrading the quality of the evidence. The small sample sizes suggests that the meta-analyses were underpowered. Understanding of the effects of interventions was also limited, as few studies reported the background diet of participants or adherence to the dietary intervention.

Conclusions

Due to a lack of published intervention evidence, conclusions cannot be drawn regarding the effect of dietary fibre or prebiotics on risk of acute diverticulitis in older adults with AS or SUDD. Although estimated effect sizes are large, there is low confidence in the body of evidence that dietary fibre supplementation may improve stool transit time and stool weight in older adults with AS or SUDD. Due to poor reporting, conclusions cannot be drawn

regarding the effect of symbiotic supplementation on GIS or bowel function. Overall, for those with AS or SUDD, a high dietary fibre intake in accordance with national gender and age specific dietary fibre intake guidelines is recommended, and dietary fibre supplementation should be considered on an individualised basis. High quality intervention evidence is needed to support evidence-based practice for the dietary management of AS and SUDD in older adults.

Author Contributions: CD, MC & FE led the design and drafting of the paper, conducting study screening and data extraction. CD, MC and WM evaluated study quality. All authors contributed to the study concept, provided revision of the manuscript and conducted the GRADE assessment. CD, MC & FE conducted this study in partial fulfilment of the Masters of Nutrition and Dietetic Practice degree.

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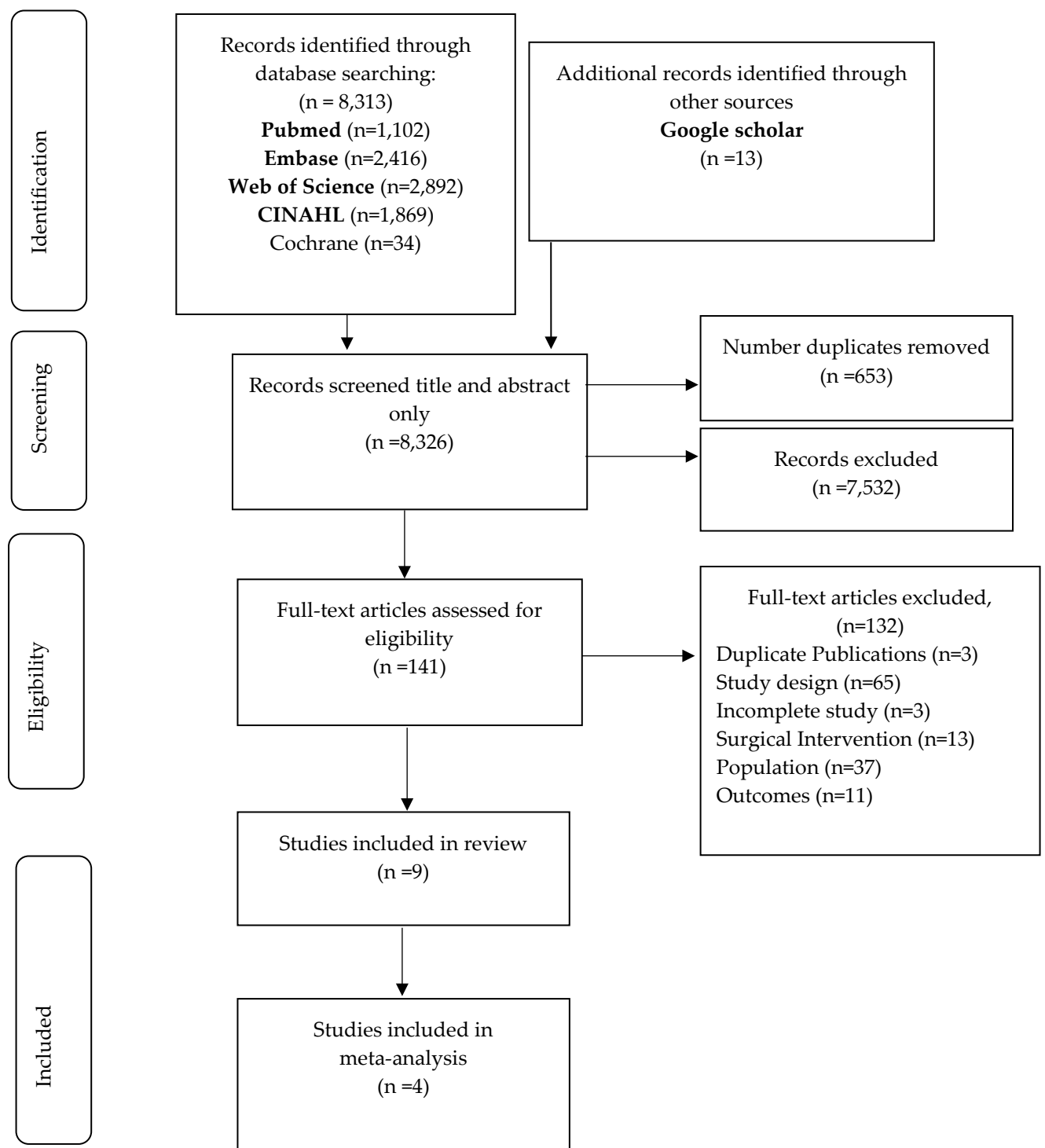


Figure 1: Flowchart of the search results and the included studies

Table 1: Study characteristics and outcomes of n=7 studies and n=8 groups of interest examining the effect of dietary fibre in the prevention of acute diverticulitis and other outcomes in those with AS or SUDD.

Study & design	Setting & population	Group of Interest / Intervention group	Comparator Group	Results
Intervention studies: dietary fibre versus placebo				
<p>Brodribb 1977 [37]</p> <p>Double blind, RCT.</p> <p>Included in MA: Yes.</p>	<p>UK n=18 (IG: n=9; CG: n=9)</p> <p>Attrition: 0%</p> <p>Background diagnosis: SUDD</p> <p>Data collected: not specified</p> <p>Female: 50%</p> <p>Mean age: 60 (range and precision estimates not specified)</p>	<p>Supplement: Bran crispbread with dietary fibre</p> <p>Dose: 9 per day, providing an additional 6.7g dietary fibre per day</p> <p>Duration: 3-months</p> <p>Background diet: No other alterations made</p>	<p>Supplement: Placebo wheat crispbread with very low dietary fibre</p> <p>Dose: 9 per day, providing an additional 0.6g dietary fibre per day</p> <p>Duration: 3-months</p> <p>Background diet: No other alterations made</p>	<p><u>Gastrointestinal symptoms: At 3-months post-baseline:</u></p> <p><i>Gastrointestinal symptom score (not validated tool; score range unknown; higher indicates worse symptoms):</i></p> <p>IG: μ8.1 (mean change -26.2) vs CG: μ35.1 (mean change -6.9); $P<0.002$ between groups.</p>
<p>Ornstein et al 1981 [36]</p> <p>Double blind, cross-over RCT.</p> <p>Included in MA: Yes.</p>	<p>UK n=76 (cross-over; n=76 for each group)</p> <p>Attrition: 24% (n=58 for each group)</p> <p>Background diagnosis: SUDD with ≥ 6 diverticula</p> <p>Data collected: not specified.</p> <p>Female: 62%</p>	<p>Supplement: Ispaghula (a.k.a. psyllium) powder + placebo wheat crispbread</p> <p>Dose: 2 sachets of powder + 8 crispbread per day, providing an additional 9.0g dietary fibre per day.</p> <p>Duration: 4-months.</p> <p>Background diet: Habitual diet and restricted from adding additional fibre</p>	<p>Supplement: Placebo wheat crispbread + placebo wheat powder, both with little dietary fibre</p> <p>Dose: 8 crispbreads and two 2 sachets of powder per day, providing an additional 2.3g dietary fibre per day</p> <p>Duration: 4-months</p>	<p><u>Gastrointestinal symptoms: At 4-months post-baseline:</u></p> <p><i>Abdominal pain score (scored 0-100; higher indicates worse symptoms):</i></p> <p>IG: μ19.5\pm18.4; mean change -3.1^a ($P>0.05$ since baseline) vs CG: μ17.5\pm15.6; mean change -5.1^a ($P>0.05$ since baseline); $P>0.05$ between groups.</p> <p><i>Lower bowel symptom score (scored 0-210; higher indicates worse symptoms):</i></p> <p>IG: μ41.3\pm27.4; mean change -6.1^a ($P>0.05$ since baseline) vs CG: μ45.0\pm28.3; mean change -2.4^a ($P>0.05$ since baseline); $P>0.05$ between groups.</p> <p><i>General symptom score (scored 0-55; higher indicates worse symptoms):</i></p>

	Median age: 64 (range 43-78 years)		Background diet: Habitual diet and restricted from adding additional fibre	<p>IG: $\mu 8.1 \pm 6.7$; mean change -1.6^a ($P > 0.05$ since baseline) vs CG: $\mu 7.6 \pm 7.3$; mean change -2.1^a ($P > 0.05$ since baseline); $P > 0.05$ between groups.</p> <p><u>Bowel habits: At 4-months post-baseline:</u></p> <p><i>Daily wet stool weight (n=57 participants per group):</i> IG: $\mu 161.0 \pm 59.8$g ($P < 0.001$ increase since baseline) vs CG: $\mu 118.8 \pm 5.4$g ($P > 0.05$ since baseline); between groups not assessed; mean changes not reported.</p> <p><i>Weekly stool frequency (n=58 participants per group):</i> IG: $\mu 11.19 \pm 3.4$ ($P < 0.001$ increase since baseline) vs CG: $\mu 9.6 \pm 2.9$ ($P > 0.05$ since baseline); between groups not assessed; mean changes not reported.</p> <p><i>Stool consistency score (range 1 to 5; 1=very hard to 5=very soft) (n=58 participants per group):</i> IG: $\mu 4.1 \pm 0.8$ ($P < 0.001$ increase since baseline) vs CG: $\mu 3.6 \pm 0.9$ ($P > 0.05$ since baseline); between groups not assessed; mean changes not reported.</p> <p><i>Stool transit time (n=39 participants per group):</i> IG: $\mu 46.9 \pm 22.9$hrs ($P > 0.05$ since baseline) vs CG: $\mu 49.9 \pm 24.4$hrs ($P > 0.05$ since baseline); between groups not assessed; mean changes not reported.</p>
		Supplement: Bran crispbread with dietary fibre + placebo wheat powder Dose: 8 crispbreads + 2 sachets of powder per day, providing an additional 7.0g dietary fibre per day. Duration: 4-months Background diet: Habitual diet and restricted from adding additional fibre	Supplement: Placebo wheat crispbread + placebo wheat powder, both with little dietary fibre Dose: 8 crispbreads and two 2 sachets of powder per day, providing an additional 2.3g dietary fibre per day Duration: 4-months Background diet: Habitual diet and restricted from adding additional fibre	<p><u>Gastrointestinal symptoms: At 4-months post-baseline:</u></p> <p><i>Abdominal pain score (scored 0-100; higher indicates worse symptoms):</i> IG: $\mu 15.2 \pm 16.9$; mean change -7.4^a ($P > 0.05$ since baseline) vs CG: $\mu 17.5 \pm 15.6$; mean change -5.1^a ($P > 0.05$ since baseline); $P > 0.05$ between groups.</p> <p><i>Lower bowel symptom score (scored 0-210; higher indicates worse symptoms):</i> IG: $\mu 39.7 \pm 27.4$; mean change -7.7^a ($P > 0.05$ since baseline) vs CG: $\mu 45.0 \pm 28.3$; mean change -2.4^a ($P > 0.05$ since baseline); $P > 0.05$ between groups.</p> <p><i>General symptom score (scored 0-55; higher indicates worse symptoms):</i> IG: $\mu 6.7 \pm 5.9$; mean change -3.0^a ($P > 0.05$ since baseline) vs CG: $\mu 7.6 \pm 7.3$; mean change -2.1^a ($P > 0.05$ since baseline); $P > 0.05$ between groups.</p> <p><u>Bowel habits: At 4-months post-baseline^b:</u></p> <p><i>Daily wet stool weight (n=57 participants per group):</i></p>

				<p>IG: $\mu 136.5 \pm 49.9$g (P<0.001 increase since baseline) vs CG: $\mu 118.8 \pm 5.4$g (P>0.05 since baseline); between groups not assessed; mean changes not reported.</p> <p><i>Weekly stool frequency (n=58 participants per group):</i></p> <p>IG: $\mu 10.3 \pm 3.0$ (P<0.001 increase since baseline) vs CG: $\mu 9.6 \pm 2.9$ (P>0.05 increase since baseline); between groups not assessed; mean changes not reported.</p> <p><i>Stool consistency score (range 1 to 5; 1=very hard to 5=very soft) (n=58 participants per group):</i></p> <p>IG: $\mu 3.8 \pm 0.8$ (P<0.001 increase since baseline) vs CG: $\mu 3.6 \pm 0.9$ (P>0.05 increase since baseline); between groups not assessed; mean changes not reported.</p> <p><i>Stool transit time (n=39 participants per group):</i></p> <p>IG: $\mu 45.3 \pm 22.4$hrs (P>0.05 increase since baseline) vs CG: $\mu 49.9 \pm 24.4$hrs (P>0.05 increase since baseline); between groups not assessed; mean changes not reported.</p>
<p>Hodgson 1977 [35]</p> <p>Double blind, cross-over RCT.</p> <p>Included in MA: Yes.</p>	<p>UK</p> <p>n=30 (cross-over data not considered as results not reported sufficiently)</p> <p>Attrition: 10% (IG: n=16; CG: n=11)</p> <p>Background diagnosis: suspected diverticular disease (Non- specific of AS or SUDD)</p> <p>Data collected: not specified.</p> <p>Female: 60%</p>	<p>Supplement: Methylcellulose (bulking agent)</p> <p>Dose: 2x500g tablets per day (1g per day)</p> <p>Duration: 3-months</p> <p>Background diet: Not described</p>	<p>Supplement: Placebo maize starch tablets (non-bulking starch).</p> <p>Dose: 2x500g tablets per day (1g per day)</p> <p>Duration: 3-months</p> <p>Background diet: Not described</p>	<p><u>Gastrointestinal symptoms: at 3-months post-baseline:</u></p> <p><i>Symptom score (ranging 0 – 50; higher indicates worse symptoms):</i></p> <p>IG: $\mu 13.0 \pm 4.2$; mean change -6.0 (P<0.01 decrease since baseline) vs CG: $\mu 16.7 \pm 8.8$; mean change -4.7 (P>0.05 since baseline); P>0.05 between groups.</p>

	Mean age: 57- 64 (range 32-85 years)			
Ewerth et al 1980 [34] Double-blind, cross-over RCT. Included in MA: Yes.	Sweden n=10 Attrition: 10% (n=9 for each group) Background diagnosis: diverticular disease and constipation (Non-specific of AS or SUDD) Data collected: not specified. Female: 67% Median age: 68 (range: 62-77 years)	Supplement: Vi-Siblin (granulate of dried ispaghula husk) Dose: 2x6g containers of powder per day (12g per day) Duration: 2-months Background diet: Not described	Supplement: Placebo lactose Dose: 2x6g in an unknown form per day (12g per day) Duration: 2-months Background diet: Not described	<u>Gastrointestinal symptoms: at 2-months post-treatment initiation:</u> <i>Flatus (incidence):</i> IG: μ 0 vs CG: μ 2; $P>0.05$ between groups; means change not reported. <i>Dyspepsia (incidence):</i> IG: μ 0 vs CG: μ 2; $P>0.05$ between groups; means change not reported. <u>Bowel habits: At 1-month post-baseline:</u> <i>Stool transit time:</i> IG: μ 72 (range 51-102hrs) vs CG: μ 63 (range 30-99hrs); $P>0.05$ between groups; means change not reported. <i>Diarrhoea (incidence):</i> IG: 0 vs CG: 1; $P>0.05$ between groups; means change not reported. <i>Constipation (incidence):</i> IG: 1 vs CG: 3; $P>0.05$ between groups; means change not reported. <i>Stool consistency (incidence of hard stools):</i> IG: 1 vs CG: 6; $P<0.05$ between groups; means change not reported. <i>Stool weight:</i> IG: μ 121g vs CG: μ 109; $P>0.05$ between groups; means change not reported. <i>Stool frequency:</i> IG: μ 0.98 movements per day vs CG: μ 1.02 movements per day; $P>0.05$ between groups; means change not reported.
Intervention studies: dietary fibre pre-test post-test.				
Brodrigg 1976 [45] Pre-test post- test, uncontrolled intervention study.	UK n=40 Attrition: 0% Background diagnosis: SUDD Data collected: not specified.	Supplement: Wheat bran Dose: 3 heaped tablespoons (approx. 24g) per day Duration: minimum 6- months; mean 8-months. Background diet: Instructed to maintain habitual diet	No comparator group.	<u>Gastrointestinal symptoms: at μ8-months post-baseline:</u> <i>Pain severity (number of patients experienced a decrease of those with symptom at baseline):</i> 91% decreased in right iliac fossa pain; 100% decreased left iliac fossa pain; 96% decreased generalised pain; 100% decreased colic pain. <i>Dyspeptic symptoms severity (number of patients experienced a decrease of those with symptom at baseline):</i>

Included in MA: No.	Female: not specified. age: not specified.			<p>86% decreased in nausea; 85% decreased in flatulence; 78% decreased in distension; 79% decreased in wind; 100% decreased in vomiting. None evaluated statistically.</p> <p><u>Bowel habits: at μ8-months post-baseline:</u> <i>Bowel symptoms severity (number of patients experienced a decrease of those with symptom at baseline):</i> 92% decreased straining; 80% decreased pain on defecation; 97% decreased hard or loose bowel motion; not evaluated statistically. <i>Wet stool weight:</i> μ89; mean change 23 (P<0.0002 increase since baseline) <i>Stool frequency:</i> n=0 had motion every \geq3days (n=5 at baseline); n=6 had motion \geq3 per day (n=18 at baseline); not evaluated statistically. <i>Stool consistency (incidence of hard stools):</i> n=2 had hard to very stools (n=25 at baseline); n=1 had liquid stool (n=7 at baseline); not evaluated statistically. <i>Stool transit time:</i> Baseline rapid transit time group: μ45hrs; mean change 24hrs. Baseline medium transit time group: μ49hrs; mean change 2hrs. Baseline slow transit time group: μ48hrs; mean change not reported (P<0.006 decreased since baseline). <u>Health service use:</u> Hospitalisation incidence: n=0</p>
<p>Thorburn et al 1992 [44]</p> <p>Pre-test post-test, uncontrolled intervention study.</p>	<p>UK n=10 Attrition: 0% Background diagnosis: SUDD Data collected: not specified. Female: 40%</p>	<p>Supplement: Ispaghula husk Dose: 2x3.5g sachet (7g total per day) Duration: 1-month Background diet: Not described</p>	No comparator group.	<p><u>Gastrointestinal symptoms: at 1-month post-baseline:</u> <i>Abdominal pain</i> 70% decreased in abdominal pain; data not reported. <u>Bowel habits: At 1-month post-baseline:</u> <i>Stool transit time:</i> IG: median 23.7hrs (range: 18.8-35.5); median change -8.8hrs (range -42.6-9.8); P<0.03 decrease since baseline</p>

Included in MA: No.	Median age: 63-70 (range 50-79 years)			
Painter et al 1972 [46] Pre-test post-test, uncontrolled intervention study. Included in MA: No.	UK n=70 Attrition: 11% (n=62) Background diagnosis: SUDD Data collected: 1967-1971. Female: 36% Mean age: 60 (range 36-82 years)	Intervention: High fibre, low-sugar diet + bran supplementation Dose: Grams per day of high fibre diet not described; bran dosage varied from 3-45g depending on patient response) Duration: 3-years and 3-months (mean 22 months adherence to bran supplementation) Background diet: N/A	No control group	<u>First diagnosis of diverticulitis: At 3-years and 3-months follow-up:</u> 1/62 <u>Gastrointestinal symptoms: at 1-month post-baseline:</u> <i>Complaint of symptom</i> 87% decrease in symptoms. <u>Bowel habits: At 3-years and 3-months follow-up:</u> <i>Stool frequency:</i> 0/62 movement <1 per day (28/62 at baseline) <u>Health service use:</u> <i>Hospitalisation incidence:</i> 3/62

SUDD, Symptomatic uncomplicated diverticular disease; MA, Meta-analysis; μ , mean; P, Probability value; UK, United Kingdom; IG,

Group of interest/intervention group; CG, control group; RCT, Randomised controlled trial; BD, twice daily

- Mean change was not reported in the study but calculated by subtracting the final outcome score from the baseline score
- Unclear if data presented is mean change or the outcome result. The table describes the value as “objective changes”; however, baseline values are not reported. The scores and results appear to be more likely to be the final result despite being described as a change.
- Sample includes two patients who had acute diverticulitis before taking bran but as they both had a normal white cell count and sedimentation rate they should be classified as having "painful diverticular disease".

Table 2: Study characteristics and outcomes of n=2 studies and n=3 groups of interest examining the effect of symbiotics on the prevention of acute diverticulitis and other outcomes in those with AS or SUDD.

Study & design	Setting & population	Group of Interest / Intervention group	Comparator Group	Results
Annibale et al 2011 [39] Three-armed RCT. Included in MA: No.	Italy n=50 (n=18 2/day probiotic group; n=16 4/day probiotic group; n=16 control group) Attrition: 14% (n=15 2/day probiotic group; n=13 4/day probiotic group; n=15 control group) Background diagnosis: SUDD Data collected: not specified. Female: 64% Mean age: 65±8.1	Symbiotic: 2.5g Lactobacillus paracasei sub. Paracasei F19(12x10 ⁹ CFU) mixed with 750g gluco-oligosaccharides, and B-group vitamins. Dose: 2x preparations per day (5g probiotic; 1.5g prebiotic). Duration: first 14-days per month for 6-months Background diet: Recommended high-fibre (>30g dietary fibre) and 1.5L water. Diet sheet given.	Supplement: None – no placebo/comparator used. Dose: N/A Duration: N/A Background diet: Recommended high-fibre (>30g dietary fibre) and 1.5L water. Diet sheet given.	First diagnosis of diverticulitis: At 6-months post-baseline: IG:0/18 vs CG: 0/16. Not compared between groups. Gastrointestinal symptoms: At 6-months post-baseline: <i>Abdominal pain (visual analogue scale; scored 0-10; higher score indicates worse symptoms):</i> IG: μ 1.9±2.2; mean change -1.8 ^a (P=0.23 since baseline) vs CG: data not reported; (P>0.05 since baseline); not compared between groups. <i>Bloating (visual analogue scale; scored 0-10; higher score indicates worse symptoms):</i> IG: μ 2.3±2.0; mean change -2 ^a (P<0.05 since baseline) vs CG: data not reported (P>0.05 since baseline); not compared between groups.
		Symbiotic: 2.5g Lactobacillus paracasei sub. Paracasei F19 (12x10 ⁹ CFU) mixed with 750g gluco-oligosaccharides, and B-group vitamins. Dose: 4x preparations per day (10g probiotic; 3g prebiotic). Duration: first 14-days per month for 6-months	Supplement: None – no placebo/comparator used. Dose: N/A Duration: N/A Background diet: Recommended high-fibre (>30g dietary fibre) and 1.5L water. Diet sheet given.	First diagnosis of diverticulitis: At 6-months post-baseline: IG:0/16 vs CG: 0/16. Not compared between groups. Gastrointestinal symptoms: At 6-months post-baseline: <i>Short-lasting abdominal pain (visual analogue scale; scored 0-10; higher score indicates worse symptoms):</i> IG: μ 0.6±0.9; mean change -1.6 ^a (P>0.05 since baseline) vs CG: data not reported; not compared between groups. <i>Bloating (visual analogue scale; scored 0-10; higher score indicates worse symptoms):</i>

		Background diet: Recommended high-fibre (>30g dietary fibre) and 1.5L water. Diet sheet given.		IG: $\mu 1.8 \pm 2.1$; mean change -2.1^a ($P < 0.05$ since baseline) vs CG: data not reported ($P > 0.05$ since baseline); not compared between groups.
Lahner et al 2012 [42] Cluster-RCT Included in MA: No.	Italy n=52 (n=30 IG; n=22 control group) Attrition: 15% (n=23 IG; n=21 CG) Background diagnosis: SUDD Data collected: not specified. Female: 67% Mean age: 66.3 ± 9.5	Symbiotic: 7g Lactobacillus paracasei B12060 (5×10^9 CFU) mixed with 700 g xylo-oligosaccharides, 500mg glutamine and 1243mg arabinoalactone. Dose: 1x preparations per day, dissolved in water. Duration: 6-months Background diet: Recommended high-fibre (>30g dietary fibre) and 1.5L water. Diet sheet and counselling given.	Supplement: None – no placebo/comparator used. Dose: N/A Duration: N/A Background diet: Recommended high-fibre (>30g dietary fibre) and 1.5L water. Diet sheet given.	First diagnosis of diverticulitis: At 6-months post-baseline: IG: 0/30 vs CG: 0/22. Not compared between groups. Gastrointestinal symptoms: At 6-months post-baseline: <i>Short-lasting abdominal pain (visual analogue scale; scored 0-10; higher score indicates worse symptoms):</i> IG: $\mu 2.2 \pm 0.8$; mean change -2.4^a ($P = 0.02$ since baseline) vs CG: $\mu 2.0 \pm 1.9$; mean change -2.6^a ($P = 0.03$ since baseline); not compared between groups. <i>Prolonged abdominal pain (visual analogue scale; scored 0-10; higher score indicates worse symptoms):</i> IG: $\mu 4.5 \pm 2.1$; mean change -2.0^a ($P = 0.052$ since baseline) vs CG: $\mu 5.5 \pm 3.5$; mean change 1.0^a ($P > 0.05$ since baseline); not compared between groups. <i>Bloating (visual analogue scale; scored 0-10; higher score indicates worse symptoms):</i> IG: $\mu 3.0 \pm 1.7$; mean change -2.3^a ($P = 0.005$ since baseline) vs CG: $\mu 2.3 \pm 1.9$; mean change -3.0^a ($P = 0.006$ since baseline); not compared between groups.

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Online Supplementary Material 1: Search strategy implemented across five electronic databases

PubMed and The Cochrane Library was searched 11 December 2018 for the following keywords (all text) and MeSH terms:

1. dietary fiber [MeSH term] OR dietary carbohydrates [MeSH term] OR fibre, dietary [MeSH term] OR prebiotics [MeSH term] OR fasting [MeSH term] OR food deprivation [MeSH term] OR diet [MeSH term]
2. fibre [keyword] OR fiber [keyword] OR carbohydrate* [keyword] OR resistant starch* [keyword] OR diet [keyword] OR dietary [keyword] OR “diet therapy” [keyword] OR “dietary therapy” OR “dietary management” [keyword] OR nutrition* management OR nutrition* therapy [keyword] OR “low residue” [keyword] OR roughage* [keyword] OR bran [keyword] OR “bowel rest” [keyword] OR “nil by mouth” [keyword] OR nbm [keyword] OR “nil per os” [keyword] OR “nothing per os” [keyword] OR fasting [keyword] OR “food deprivation” [keyword] OR starvation [keyword] OR prebiotic* [keyword] OR “diet restriction” [keyword] OR “conservative treatment” [keyword] OR “conservative therapy” [keyword] OR “conservative management” [keyword]
3. 1 OR 2
4. diverticulitis [MeSH term] OR diverticulum [MeSH term] OR diverticulosis, colonic [MeSH term] OR diverticulum, colon [MeSH term]
5. divertic* [keyword]
6. 4 OR 5
7. 3 AND 6

CINAHL(via Ebscohost) was searched 11 December 2018 using the following keywords and CINAHL Headings:

1. dietary fiber[exp][CINAHL term] OR dietary carbohydrates[exp][CINAHL term] OR prebiotics[exp] [CINAHL term] OR fasting[exp] [CINAHL term] OR restricted diet [exp][CINAHL term] OR diet[exp][CINAHL term]
2. fibre [keyword] OR fiber [keyword] OR carbohydrate* [keyword] OR “resistant starch*” [keyword] OR diet [keyword] OR dietary [keyword] OR “dietary therapy” OR “dietary management” [keyword] OR nutrition* management[keyword] nutrition* therapy [keyword] OR “low residue” [keyword] OR roughage* [keyword] OR bran [keyword] OR “bowel rest” [keyword] OR “nil by mouth” [keyword] OR nbm [keyword] OR “nil per os” OR “nothing per os” [keyword] OR restricted diet [keyword] OR fasting [keyword] OR “food deprivation” [keyword] OR starvation [keyword] OR prebiotic* [keyword] OR “conservative treatment” [keyword] OR “conservative therapy” [keyword] OR conservative management” [keyword]
3. 1 OR 2
4. Diverticulitis[exp][CINAHL term] OR diverticulum[exp] [CINAHL term] OR diverticulum, colon[exp] [CINAHL term]
5. divertic* [keyword]
6. 4 OR 5
7. 3 AND 6

Embase was searched 11 December 2018 using the following search terms:

1. dietary fiber [exp][Emtree term] OR carbohydrate diet[exp][Emtree term] OR prebiotic agent[exp][Emtree term] OR diet restriction[exp][Emtree term] or food deprivation[exp][Emtree term] OR roughage[exp][Emtree Term] OR bran[exp][Emtree term] OR conservative treatment[exp][Emtree term] OR diet [exp][Emtree term]
2. fibre [keyword] OR fiber [keyword] OR carbohydrate*[keyword] OR “resistant starch*” [keyword] OR diet [keyword] OR dietary [keyword] OR “dietary therapy” [keyword] OR

“dietary management” [keyword] OR nutrition* management [keyword] nutrition* therapy [keyword] OR “low residue” [keyword] OR “bowel rest” [keyword] OR “prebiotic agent” [keyword] OR “nil by mouth” [keyword] OR nbm [keyword] OR “nil per os” [keyword] OR “nothing per os” [keyword] OR diet restriction [keyword] OR roughage* OR bran [keyword] OR fasting [keyword] OR “food deprivation” [keyword] OR starvation [keyword] OR prebiotic* [keyword] OR “conservative treatment” [keyword] OR “conservative therapy” [keyword] OR conservative management” [keyword]

3. 1 OR 2
4. diverticulitis [exp][Emtree term] OR diverticulosis [exp][Emtree term] OR colon diverticulosis [Emtree term]
5. divertic* [keyword]
6. 4 OR 5
7. 3 AND 6

Web of science was searched 11 December 2018 using the following keywords:

1. dietary fiber OR dietary carbohydrates OR fibre, dietary OR prebiotics OR fasting OR food deprivation
2. fibre OR fiber OR carbohydrate* OR “resistant starch*” OR diet OR dietary OR “dietary management” OR “nutritional management” OR “low residue” OR roughage* OR bran OR “bowel rest” OR “nil by mouth” OR nbm OR “nil per os” OR “nothing per os” OR fasting OR “food deprivation” OR starvation OR prebiotic* OR “diet restriction” OR “conservative treatment” OR “conservative therapy” OR conservative management”
3. 1 OR 2
4. diverticulitis OR diverticulum OR diverticulosis, colonic OR diverticulum, colon
5. divertic*
6. 4 OR 5
7. 3 AND 6

Online Supplementary Material 2: GRADE Evidence Table for the evaluation of interventions to manage diverticular disease

Question: Dietary fibre supplements compared to placebo or no intervention for managing diverticular disease

Setting: Patients with diagnosed diverticular disease (diverticula present in colon)

Quality assessment							№ of patients		Effect	Quality
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	dietary fibre supplements	placebo or no intervention	Absolute (95% CI)	
Gastrointestinal symptoms (assessed with: symptom rating scale (not validated))										
3 (4 intervention groups)	randomised trials	serious ^a	not serious	not serious	serious ^b	none	83	78	SMD 0.13 SD lower (31 lower to 0.05 higher)	⊕⊕○○ LOW
Bowel habits: stool weight (assessed with: grams)										
2	randomised trials	serious ^a	not serious	not serious	very serious ^c	strong association	66	66	MD 42 grams higher (26 higher to 57 higher)	⊕⊕○○ LOW
Bowel habits: transit time (assessed with: hours)										
2	randomised trials	serious ^a	not serious	not serious	very serious ^{b,c}	all plausible residual confounding would suggest spurious effect, while no effect was observed	87	48	MD 3.7 hours lower (11.06 lower to 3.65 higher)	⊕⊕○○ LOW

CI: Confidence interval; **SMD:** Standardised mean difference; **MD:** Mean difference

a. As assessed by the Cochrane Risk of Bias Tool (Figure 1; Online Supplementary Material 1)

b. The confidence interval is substantial

c. Although the confidence intervals are not wide; there is only a small number of participants which is largely made up of cross-over trial participants. This leads to decreased confidence that there is no substantial imprecision.

Question: Symbiotic supplementation compared to no intervention for diverticular disease

Setting: Patients with diverticular disease (diverticula in the colon)

Quality assessment							№ of patients		Effect		Quality
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Symbiotic supplementation	no intervention	Relative (95% CI)	Absolute (95% CI)	
Gastrointestinal symptoms (assessed with: Symptom rating scales (not validated))											
3	randomised trials ^a	very serious _b	not serious	not serious	very serious _c	none	109	37	Not pooled	Not pooled	⊕○○○ VERY LOW

CI: Confidence interval

a. One RCT, one cluster-RCT and one randomised intervention study

b. Assessed according to the Cochrane Risk of Bias tool (Online Supplementary Material 1)

c. Although not pooled; measures of precision are large in individually reported outcomes. The studies also have small sample sizes further decreasing confidence in the precision of the reported effect sizes.